REMARKS/ARGUMENTS

Upon entry of the above claim amendments, Claims 1-13 are currently pending in the present application.

Claims 11-13 are new. Support for Claim 11 can be found throughout Applicants' specification, for example, at lines 3-5 of page 4 and Example 3 of page 7 of the application as filed. Support for Claim 12 can be found, for example, at lines 9-11 of page 4 and Examples 1 and 2 of page 6 of the application as filed. Support for Claim 13 can be found throughout Applicants' specification, for example, at lines 13-27 of page 1, lines 1-9 of page 2, and lines 3-8 of page 5.

No new matter has been introduced in the above claim amendments.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections and the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as the application is in condition for allowance.

Priority Document

The Office Action has acknowledged Applicants' claim for foreign priority. The Office Action also acknowledges receipt of the certified copies of Applicants' priority document from the International Bureau. Applicants hereby thank the Examiner.

However, the Office Action states that an English translation of the priority document (i.e., German Patent Application No. 10215942.4) is not of record. For this purpose, Applicants hereby state that the present application as filed is the English language translation of the priority document. Accordingly, the present application is entitled to the priority date of April 11, 2002, which is the filing date of German Patent Application No. 10215942.4.

Rejections under 35 U.S.C. 102 (a)

Claims 1 to 3 have been rejected under 35 U.S.C. 102 (a) as allegedly being anticipated by Mauler et al. (J. Pharmacol Exp. Ther., 2002, Vol. 302, No. 1; hereinafter "Mauler"). Applicants note that the Mauler was published online on June 13, 2002 and mailed on June 14, 2002 (as indicated in the Office Action at page 2).

Applicants respectfully submit that Mauler is not a proper reference under 35 U.S.C. 102(a). As previously discussed, the instant application is entitled to a priority date of **April 11, 2002**, which antedates Mauler. Accordingly, Mauler is not a prior art to this application. Therefore, the rejection under section 102 (a) is improper and has been traversed.

Rejections under 35 U.S.C. 103(a)

Claims 1-4, 8 and 9 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Mauler in view of Szabo et al. (J. Pharmacol. Exp. Ther., 2001, 297:819-826; hereinafter "Szabo"). Applicants respectfully traverse.

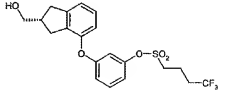
As above stated, Mauler, which is cited by the Office as the primary reference, cannot be used to support a rejection under Section 103(a) because, as above stated, it is not a prior art to the present application. Applicants submit that something that does not qualify as a prior art cannot form the basis of a Section 103 rejection. With Mauler being disqualified as a prior art, Applicants further submit that Szabo cannot support an obviousness rejection under 35 U.S.C. 103(a).

The present invention is directed to an aqueous formulation of (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate (Compound (I)) and cyclodextrin. The instant claims further recite specific concentration ranges of Compound (I) and cyclodextrin in the formulation (as recited in Claims 2-4), or additional component in the formulation (as recited in Claims 8 and 9).

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as

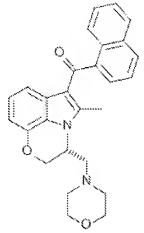
"impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

Applicants respectfully submit that Szabo does not disclose or teach Compound (I), let alone an aqueous formulation comprising Compound (I) and cyclodextrin. As a matter of fact, Szabo only discloses using an aqueous solution comprising cyclodextrin as a suitable vehicle for infusing WIN 55,212-2 and CP 55,940 (*See* page 4 of the Office Action). Indeed, Compound (I) of the present application is structurally unrelated to WIN 55,212-2 and CP 55,940. To evidence the structural dissimilarity between Compound (I) as compared to WIN 55,212-2 and CP 55,940, each of their structures are presented as follows:

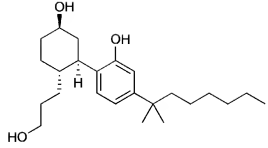


Compound (I) of the present invention

[(-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate]



WIN 55,212-2



CP 55,940

Clearly, Compound (I) is fundamentally different in structure from WIN 55,212-2 and CP 55,940. Further, as supported by the now-disqualified Mauler reference, Compound (I) (as BAY 38-7271 in Mauler) "is a new high-affinity cannabinoid receptor subtype 1 (CB1 receptor) ligand…**structurally unrelated to any cannabinoid receptor ligand known so far**" (*See* Abstract of Mauler).

Therefore, Applicants respectfully submit that Szabo does not teach or suggest Compound (I), let alone an aqueous formulation comprising Compound (I) and cyclodextrin. Nothing in Szabo would have led a skilled artisan to arrive at the present invention. Accordingly, the rejections of Claims 1-4, 8 and 9 under 35 U.S.C. 103 (a) are improper and traversed herein. Therefore, reconsideration and withdrawal of the 35 U.S.C. 103 (a) rejections is respectfully requested.

Claims 1-9 have been rejected under 35 U.S.C 103 (a) as allegedly being unpatentable over Mauler in view of Szabo and Nakazi (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000; hereinafter "Nakazi"). As above stated, Mauler, which is cited by the Office as the primary reference, is not a prior art to the present application. Further, Applicants respectfully submit that Szabo and Nakazi are insufficient to support a rejection under 35 U.S.C 103 (a).

Besides the above discussions, the instant claims further recite pH values of the present formulation (Claim 5), or additional component such as a physiologically tolerated acid (Claims 6 and 7).

The above statements are applicable in discussing the differences between the present invention and Szabo's disclosure.

Applicants also submit that the disclosure of Nakazi does not cure the deficiencies in Szabo. As a matter of fact, Nakazi only discloses the use of a citrate buffer at pH 4.8 as a vehicle for cerebral infusion of WIN 55,212-2 and CP 55,940. Nakazi does not teach or suggest Compound (I), let alone an aqueous formulation comprising Compound (I) and cyclodextrin. Accordingly, Applicants submit that: first, neither Szabo nor Nakazi teaches or suggests Compound (I), or its aqueous formulation with cyclodextrin; second, neither Szabo nor Nakazi provides any motivation, teaching or suggestion for formulating Compound (I) with cyclodextrin; and third, nothing in Szabo or Nakazi would have led a skilled artisan to arrive at the present invention. Therefore, the rejections of Claims 1-9 under 35 U.S.C. 103 (a) are improper and traversed herein. Accordingly, reconsideration and withdrawal of the 35 U.S.C. 103 (a) rejections is respectfully requested.

Claims 1-4 and 8-10 have been rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Mauler in view of Szabo and Yamada (U.S. Patent No. 5,807,337; hereinafter "Yamada"). As above stated, Mauler, which is cited by the Office as the primary reference, is now disqualified as a prior art to the present application. Further, Applicants respectfully submit that Szabo and Yamada are insufficient to support a rejection under 35 U.S.C 103 (a).

The recitations of claims 1-4 and 8-9 are the same as above. Additionally, Claim 10 recites a kit having a container including the instantly claimed formulation, and an infusion apparatus.

Applicants submit that the disclosure of Yamada does not cure the deficiencies in Szabo. Yamada only discloses the use of a plastic infusion apparatus for the continuous administration of therapeutic agents. Yamada does not teach or suggest Compound (I), let alone an aqueous formulation comprising Compound (I) and cyclodextrin. In brief, Applicants submit that: first, neither Szabo nor Yamada teaches or suggests Compound (I), or its aqueous formulation with

cyclodextrin; second, neither Szabo nor Yamada provides any motivation, teaching or suggestion for formulating the claimed Compound (I) with cyclodextrin; and third, nothing in Szabo or Yamada would have led a skilled artisan to reach the present invention. Accordingly, the rejections of Claims 1-4 and 8-10 under 35 U.S.C. 103 (a) are improper and traversed herein. Therefore, reconsideration and withdrawal of the 35 U.S.C. 103 (a) rejections is respectfully requested.

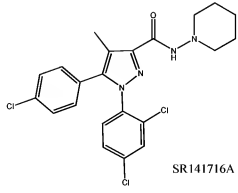
Claims 1-4, 8 and 9 have been rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Mittendorf *et al.* (U.S. Patent No. 6,262,112; hereinafter "Mittendorf") in view of Szabo. The Examiner alleged that it is obvious to a skilled artisan to modify the Mittendorf formulation with the aqueous cyclodextrin solution in Szabo to arrive at the instantly claimed formulation. Applicants respectfully disagree.

It was discovered by the present inventors that aqueous formulations of Compound (I) show an inhomogenous concentration distribution, which means that infusion of the compound, especially at low active ingredient concentrations, at a constant rate over time cannot ensure administration of constant dosage levels of the compound (*See* lines 21 to 25 at page 1 of the instant application). The inventors surprisingly discovered that the addition of cyclodextrin to an aqueous formulation of Compound (I) led to uniform concentrations of the compound (*See* lines 5 to 6 at page 2 of the application). As such, the present invention is directed to an aqueous formulation comprising Compound (I) and cyclodextrin. In contrast, Mittendorf does not disclose cyclodextrin, let alone any aqueous formulation comprising Compound (I) and cyclodextrin.

While Szabo discloses WIN 55,212-2 and CP 55,940 in a combination with cyclodextrin, these Szabo compounds are fundamentally different in structure from Compound (I), as previously discussed. Having noted that Compound (I) is structurally unrelated to WIN 55,212-2 and CP 55,940, the Examiner nevertheless alleged that the pharmacological interaction between Compound (I) and a specific receptor is similar to that between each of the above-mentioned Szabo compounds and the receptor (*See* page 12 of the Office Action). Applicants respectfully disagree.

Applicants submit respectfully that the instant pharmacological interaction would be expected to be different from that between a Szabo compound and the receptor. As stated by the Examiner, the structural relationship between a compound and a receptor is "based on principles of physical organic chemistry, such as size of the molecule and polarity of the molecule" (*See* page 12 of the Action). Clearly, the polarity of Compound (I) is different from that of the Szabo compounds. For example, one skilled artisan would expect that the polarity of CP 55,940 is not anywhere similar to that of Compound (I), due to, at least in part that CP 55,940 has three polar hydroxyl groups in its structure, while Compound (I) has only one hydroxyl group. Further, the polarity of Compound (I) is different from that of WIN 55,212-2, since WIN 55,212-2 has no hydroxyl group or similar moieties in its structure. Indeed, one skilled in the art would expect that physical organic chemical properties of Compound (I) and the Szabo compounds are dissimilar. Accordingly, the pharmacological interaction between Compound (I) and the receptor would also be different from that between a Szabo compound and the same receptor.

Applicants further submit that Szabo does not provide any motivation or suggestion for combining cyclodextrin with Compound (I) as disclosed in Mittendorf. Although Szabo discloses aqueous formulations of cyclodextrin and two cannabinoid receptor antagonists (i.e., WIN 55,212-2 and CP 55,940), it also indicates that cyclodextrin is not desirable in a formulation comprising a third cannabinoid receptor antagonist (i.e., SR141716A) (*See* p. 820 of Szabo). The structure of SR14716A is as follows:



SR141716A

(*see* M. Rinaldi-Carmona *et al.*, *FEBS Letters* 350 (1994), 240-244). Szabo discloses that SR141716A is dissolved in 50% ethanol (v/v in saline), without cyclodextrin being used as a co-solvent. Clearly, Szabo demonstrates that a good solvent for certain cannabinoid receptor antagonists may not be a good solvent for other cannabinoid receptor antagonists. Further, in view of the fact that the above-mentioned cannabinoid receptor antagonists have distinct chemical structures from each other, it would be impossible for a skilled artisan, based on the Szabo disclosure, to predict a suitable solvent for one particular compound simply based on a test result for a different compound. Thus, given the distinct structural features and pharmacological properties of Compound (I) as above discussed, one skilled in the art would not be motivated to use cyclodextrin as a solvent for Compound (I). Even assuming, *in arguendo,* that one were to make such a formulation, there would have been no reasonable expectation of success in the art that cyclodextrin would be a good solvent for Compound (I).

Further, it is a well-settled rule that an invention ***cannot*** be assembled by picking and choosing elements from the prior art using the claims in the present application as a "blue print." There must be some ***reason*** for the combination other than the hindsight obtained from the invention itself (*See Interconnect v. Feil,* 774 F.2d 1132 at 1143 (*Fed Cir.* 1985)). Here, the Examiner has failed to supply that reason. In the absence of such a reason or motivation, Applicants submit that the Examiner's rejections are nothing more than the result of hindsight reconstruction of the invention based ***solely*** on Applicants' teachings.

Therefore, Applicants respectfully submit that: first, there is no suggestion or motivation in either Mittendorf or Szabo to formulate Compound (I) with cyclodextrin (as directed by the present invention); second, there would have been no reasonable expectation of success to a skilled artisan due to Compound (I)'s distinctiveness in structural and pharmacological properties; and third, the Examiner's choice of elements from the prior art to obtain the present invention is impermissible hindsight. Accordingly, the formulation of the present invention is indeed patentable over

Mittendorf in view of Szabo. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. 103 (a) on Claims 1-4, 8 and 9 is respectfully requested.

Claims 1-9 have been rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Mittendorf in view of Szabo and Nazaki. Applicants respectfully traverse.

As above-discussed, Nakazi only discloses additionally the use of a citrate buffer at pH 4.8 as a vehicle for cerebral infusion of WIN 55,212-2 and CP 55,940. Nakazi does not cure the deficiencies in Mittendorf and/or Szabo, as that Nakazi does not provide any motivation or suggestion for arriving at the present invention. Accordingly, the present invention is non-obvious over Mittendorf in view of Szabo and Nakazi. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. 103 (a) on Claims 1-9 is respectfully requested.

Claims 1-4, and 8-10 have been rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Mittendorf in view of Szabo and Yamada. Applicants respectfully traverse.

As above-discussed, Yamada only discloses additionally the use of a plastic infusion apparatus for the continuous administration of therapeutic agents. Yamada does not teach or suggest the use of compound (I), let alone an aqueous formulation of Compound (I) and cyclodextrin. Further, Yamada cannot cure the deficiencies in lacking of motivation or suggestion in Mittendorf and/or Szabo. Accordingly, the present invention is indeed patentable over Mittendorf in view of Szabo and Yamada. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. 103 (a) on Claims 1-9 is respectfully requested.

CONCLUSIONS

In view of the remarks made herein, the present application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105, Order No. 80741 (303989).

Dated: December 29, 2008

Respectfully submitted,

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